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Mini review

Interleukin-15: New kid on the block for antitumor combination therapy

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ABSTRACT

Interleukin (IL)-15 is one of the most promising molecules to be used in antitumor immune therapy, as it is able to stimulate the main killer cells of both the innate and adaptive immune system. Although this cytokine can be used as a stand-alone immunotherapeutic agent, IL-15 will probably be most efficient in combination with other strategies to overcome high tumor burden, immune suppression of the tumor microenvironment and/or the short half-life of IL-15. In this review, we will discuss the combination strategies with IL-15 that have been tested to date in different animal tumor models, which include chemotherapy, other immunostimulatory cytokines, targeted therapy, adoptive cell transfer and gene therapy. In addition, we give an overview of IL-15 combination therapies that are currently tested in clinical studies to treat patients with hematological or advanced solid tumors.

1. Background

Since its discovery two decades ago, interleukin (IL)-15 has become one of the most promising molecules for antitumor immunotherapy, illustrated by its top position in the US National Cancer Institute's ranking of 20 immunotherapeutic drugs with the greatest potential for broad usage in cancer therapy [1]. IL-15 owes its nomination to its ability to stimulate both the innate and the adaptive immune system. More specifically, IL-15 is a pivotal factor on one hand in the development, proliferation and activation of natural killer (NK) cells, and on the other hand in $CD8^+$ T-cell proliferation and activation [2,3]. On top, IL-15 is also a main player in the activation of NKT cells, γδ T cells, B cells and increases the antibody-secreting capacity of the latter [4–6]. Due to its pleiotropic functions, IL-15 forms a bridge between both immune systems, which is in favor of optimal defense against malignant cells [7].

At its discovery, IL-15 was thought to exert similar functions as IL-2, because both cytokines share the β- and common γ-chains of their receptor, which contains the cytoplasmic motifs required for signal transduction. Interestingly however, IL-2 and IL-15 display different functions *in vivo*, which may be due to the α-moiety of the respective receptors [8–10]. In addition to activating $CD8^+$ T cells, IL-2 causes activation-induced cell death and provokes maintenance of $CD4^+$ $CD25^+$ regulatory T cells, in contrast to IL-15 [11,12]. These unique properties of IL-15 may be of benefit in the immunotherapy of cancer [8]. Indeed, IL-15-mediated immune stimulation occurs mainly by a unique *trans*-presentation mechanism, whereby IL-15 bound to the α-moiety of the IL-15 receptor (IL-15Rα) is being *trans*-presented to the βγ-chains of its receptor on neighboring cells [13–15]. In addition, IL-15 can bind to the IL-15 βγ-receptor without forming a pre-complex with IL-15Rα, although with a lower binding affinity [16]. Moreover, pre-complexation of IL-15 with IL-15Rα results in an increase of the IL-15 half-life [17,18]. The different binding strategies of IL-15 to its receptor subunits are depicted in Fig. 1. Since both NK cells and $CD8^+$ T cells as the main killers of malignant cells express IL-15 βγ-receptor, IL-15 is considered to be an important mediator of antitumor immunity.

IL-15 has proven to possess immunostimulatory capacities both *in vitro* and in preclinical models. Therefore, IL-15 has recently been incorporated in three phase I clinical trials as a single agent to

Abbreviations: ALT-803, IL-15 + sushi domain of IL-15Rα; BMT, bone marrow transplantation; CTLA, cytotoxic T lymphocyte antigen; CTVT, canine transmissible venereal tumors; DC, dendritic cells; EGFR, epidermal growth factor receptor; GVHD, graft-versus-host disease; GVT, graft-versus-tumor; IL, interleukin; IL-15R, IL-15 receptor; MDSC, myeloid-derived suppressor cells; moABs, monoclonal antibodies; NK, natural killer; PD1, programmed cell death 1; RFA, radiofrequency thermal ablation; rh, recombinant human; TGF, transforming growth factor; Th, T helper.

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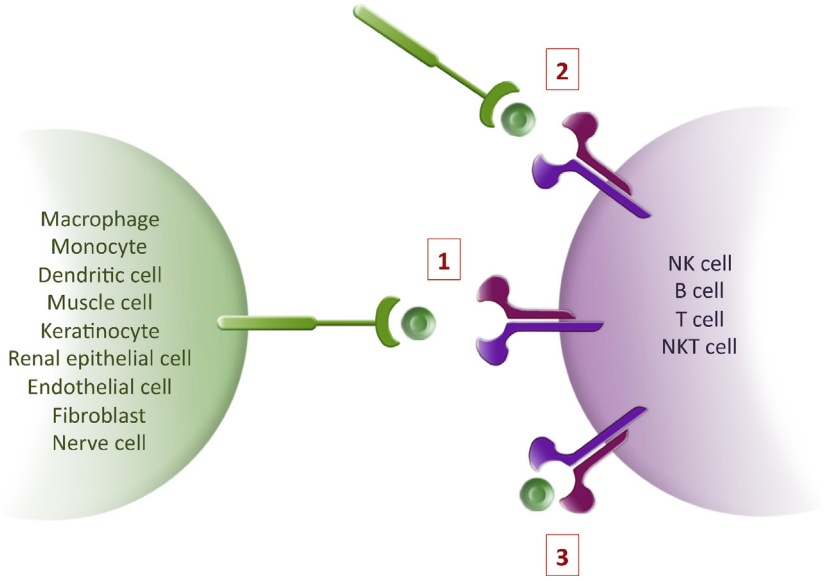

Fig. 1. Mechanisms whereby IL-15 can bind to its effector cells. IL-15 can be presented by the IL-15Rα-moiety (green) to the IL-15Rβγ-subuntis (purple) in a membrane-bound state through a process called transpresentation (1) or in a soluble state (2). IL-15 can also bind the IL-15Rβγ-subunits directly, but with a lower affinity (3).

treat multiple types of advanced solid tumors (NCT01727076, NCT01021059, NCT01572493). Most likely, combining IL-15 with agents that work synergistically to activate immunity or deplete immune-regulating/suppressing cells may result in more vigorous immune responses and improved clinical outcome [19]. In this regard, IL-15 can be combined with strategies to (i) overcome high tumor burden, (ii) further strengthen the antitumor immune response and/or (iii) block inhibitory strategies which are used by tumors to promote their survival. In this review, we discuss the therapeutic combination strategies with IL-15 examined to date in animal tumor models. Furthermore, we summarize ongoing clinical trials that test recombinant human (rh)IL-15 as an (adjuvant) therapy in combination with other antitumor therapies.

2. Lessons from preclinical tumor models

IL-15 as immunotherapeutic agent is an excellent adjuvant as observed in mouse, beagle and rat tumor models (Table 1). In these studies, IL-15 is combined with other antitumor strategies, namely (i) chemotherapeutic agents, (ii) immunosuppressors, (iii) other cytokines, (iv) DNA- or tumor vaccines (v) immune-activating antibodies, (vi) inhibitory antibodies of immune-suppressive molecules or (vii) adoptive cell therapy.

2.1. Chemotherapy

Nowadays, first-line treatment of most cancers consist of surgery, chemotherapy, radiotherapy or a combination of these. Although in most cases the tumor burden is reduced significantly, chemotherapy/radiotherapy-resistant remnant tumor cells contribute to a high relapse rate of tumor patients. Therefore, adjuvant immunotherapy is currently intensively being investigated to improve treatment outcome of tumor patients by eliminating chemotherapy-resistant tumor cells using the patient's own immune system. Interestingly, some chemotherapeutic agents can stimulate a process called 'immunogenic cell death', in which tumor cells undergo apoptosis while emitting a combination of signals that can elicit a long-term protective antitumor immune response [20–22]. Five agents causing immunogenic cell death have been identified to date, including cyclophosphamide [23]. In addition, many other chemotherapeutics, such as 5-fluorouracil, can modulate the tumor's phenotype (e.g. upregulating carcinoembryonic antigen and downregulating Bcl2 expression), rendering them more sensitive to immune-mediated killing [24,25]. In this context, IL-15 as a potent immunostimulatory molecule may act synergistically with chemotherapeutic agents by repairing or strengthening the antitumor functions of immune effectors that are involved in the patient's response to chemotherapy (Fig. 2).

IL-15 has been tested in combination with (1) cyclophosphamide; and (2) 5-fluoruracil and leucovorin. The combination therapy with cyclophosphamide, an alkylating cytotoxic chemotherapeutic, and IL-15 resulted in a prolonged survival of both C57BL/6J mice bearing rhabdomyosarcoma [26] and established pulmonary metastases [27]. The prolonged survival following treatment with the combination therapy may be due to an increased percentage of $NK1.1^+/LGL^+$ cells and $CD8^+/CD44^+$ memory T cells in the blood as compared with chemotherapy alone. Interestingly, the interaction between NK cells, which displayed an improved cytotoxicity profile after the combination therapy, and T cells was required to improve the survival, while the presence of B cells deteriorates this effect, as shown in B-cell depleted mice [26,27]. Also in colorectal cancer, chemotherapy in combination with IL-15 was efficacious. Here, the adjuvant IL-15 potentiates the antitumor activity of 5-fluorouracil alone or in combination with leucovorin [28]. IL-15 induced a significant decrease in chemotherapy-induced gastrointestinal toxicities and reduced the tumor weight in the combination therapy [28].

In all three studies, the statistically significant reduction in tumor growth after combination therapy of chemotherapeutics and IL-15 might be explained by the principle of 'immunogenic cell death' and the increased immune effector functions of $CD8^+$ T cells and NK cells.

2.2. Radiofrequency thermal ablation/bone marrow transplantation

Taking into account the chemotherapy-resistance of some tumor cells, not only adjuvant treatments, but also alternative treatments for chemotherapy are being pursued to broaden the treatment options of tumor patients. A possible alternative is the use of radiofrequency thermal ablation (RFA) to kill tumor cells (Fig. 2). While the technique is safe and partly effective in